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Informative Morphogenetic and Phenogenetic Variants in Children With Cleft Lip/Cleft Palate

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In 230 patients with nonsyndromic cleft lip/cleft palate (138 boys and 92 girls) and in 226 age related healthy children (137 boys and 89 girls) informative morphogenetic and phenogenetic variants (IMV and PHV, respectively) were investigated. There was no difference between the number of IMVs between both groups (χ^2 = 5.89; d.f. = 3; α > 0.70). This finding is in line with the hypothesis that facial cleft disorders occur during blastogenesis, whereas IMVs and PHVs are typical patterns of the embryo- and fetogenesis. The anthropometric findings are contradictory. In a few non-craniofacial phenogenetic variants significant differences were found between the patients and the healthy children. Intrinsic factors or secondary sequelae of the primary defect might additionally act in the morphological fine tuning of children with single cleft lip/cleft palate. © 1996 Wiley-Liss, Inc.

KEY WORDS: cleft lip/cleft palate, informative morphogenetic variants, phenogenetic variants

INTRODUCTION

Cleft lip/cleft palate occurs either in non-syndromal or in syndromal forms. Facial cleft defects result from an error in morphogenesis during late blastogenesis and early embryogenesis due to a failure of fusion of both the symmetrical organ anlagen of the primary or secondary palate. Informative morphogenetic [IMVs; Pinsky, 1985a,b] and phenogenetic variants [PHVs; Opitz 1986] are typical outcomes of embryo- and fetogenesis, respectively [Opitz, 1986]. Thus, it seems highly unlikely that in isolated facial cleft defects an increased number of them may be observed.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

Until now, this theoretically clear hypothesis was confirmed by the analysis of a small number of associations as the typical pattern of blastogenesis [Opitz, 1993, 1995]. Even the number of those disorders exactly evaluated with regard to IMVs and PHVs is relatively limited. Merely based on subjective clinical experience it is almost accepted, that IMVs and PHVs do not play any important diagnostic role in these disorders of the very early stages of embryonic development. That was the reason why children with cleft lip/cleft palate as a disorder per se had been systematically investigated to answer the question whether or not there is an increased number of IMVs and PHVs, respectively.

SUBJECTS AND METHODS

Two hundred thirty patients with facial cleft disorders (138 boys, 92 girls) and 226 healthy children (137 boys, 87 girls) were investigated. They were between 0.25 and 16 years old. There was no statistical difference for age and sex (χ^2 = 21.94; d.f. = 42; α > 0.99). Thus, the distribution of patients is to consider homogeneous and consequently, these groups are comparable with each other. The detailed distribution of the patients and the healthy controls is summarized by the sex and age (Table I).

Altogether, 40 informative morphogenetic variants were examined qualitatively (see Appendix). Most of them were craniofacial anomalies (n = 19; 0.48); 6 of them were evaluated at the trunk (0.15) , and 13 in limbs, namely, 5 in hands (≈0.13) and 8 in feet (≈0.20).

Moreover, using anthropometric techniques, 20 phenogenetic variants were evaluated quantitatively, and seven anthropometric indices were calculated [Knussmann, 1985; Farkas and Munro,1987; Méhes, 1986].

For statistical calculations the classic χ^2-test and the *t*-test were used. Furthermore, the multiple *t*-test as well as the regression analysis with *z*-transformation of correlation coefficients were applied with the transformation of sum frequencies into probits [Sachs, 1992; Weber, 1980]. *Z*- and probit values were taken from the literature [Wissenschaftliche Tabellen Geigy, 1980]. The years of age were transformed into logarithms to the base 10.

TABLE I. Distribution of Patients With Cleft Lip/Cleft Palate and Healthy Controls by Age and Sex*

Age (years)	Patients		Controls	
	Boys	Girls	Boys	Girls
0.25	15	8	11	5
0.5	11	7	9	6
1.0	18	12	19	10
2.0	25	9	18	8
3.0	6	4	10	10
4.0	7	11	13	7
5.0	10	8	8	8
6.0	9	9	10	6
7.0	12	6	5	5
8.0	6	3	6	5
9.0	4	3	4	2
10.0	3	3	6	3
11.0	3	1	4	4
12.0	5	5	3	1
13.0	4	2	3	2
14.0	—	—	4	4
15.0	—	—	2	1
16.0	1	—	2	2
Total	138	92	137	89

*$X^2 = 21.94$; d.f. = 42; $\alpha > 0.99$.

RESULTS

In the group of patients altogether 116 IMVs were observed. There was no difference in the appearance of IMVs between boys and girls as well as their specifically topographical distribution ($\chi^2 = 4.41$; d.f. 6; $\alpha > 0.50$).

In the control groups of both sexes altogether 87 topographically identically distributed IMVs were registered ($\chi^2 = 2.55$; d.f. 4; ($\alpha > 0.70$). Both in the patients and in the control group epicanthus is most often seen at frequencies of 38.6% and 58.6%, respectively.

Due to this high prevalence of epicanthal folds in both groups the cranio-facial anomalies amount to the first rank by $n_1 = 73$ (≈ 0.63) and $n_2 = 70$ (≈ 0.81) of all the IMVs tested. Based on 26 truncal anomalies in both sexes they are located at the second rank (≈ 0.22) in the patient group and at the third rank in the control group based on six anomalies (≈ 0.69). In patients with cleft lip/cleft palate the anomalies on the hands and feet ($n = 17$; ≈ 0.15) were ranked in the third position. In the healthy control children hand anomalies ($n = 11$; ≈ 0.13) led to the second position prior to the truncal anomalies ($n = 6$; ≈ 0.69).

TABLE II. Number of Informative Morphogenic Variants (IMV) in Children With Cleft Lip/Cleft Palate (n = 230) and in Healthy Boys and Girls as Controls (n = 226)*

Number of IMV	Patients (n)	Healthy controls (n)
0	140	147
1	67	71
2	20	8
3	3	0

*$X^2 = 5.89$; d.f. = 3; $\alpha > 0.70$.

The numerical distribution of IMVs in both the investigation group and in healthy controls is summarized in Table II.

Although there are three girls with three IMVs in the investigation group and none in the control group this difference was not significant ($\chi^2 = 5.89$; d.f. 3; $\alpha > 0.70$).

Using the multiple *t*-test, on the average, significant findings were found for the anthropometic *craniofacial* indices summarized in Table III.

Calculating *non-craniofacial* PHVs, on the average, we found statistically significant differences between the circumference of chest, of the intermamillary distance, and of the length of hand in both the affected and non-affected boys and girls. No difference could be calculated for the length of sternum ($\alpha > 0.50$), and the length of middle finger was statistically significant only in boys (Table IV).

The findings of probit regression analyses are contradictory. For instance, with regard to the circumference of chest the differences between boys and girls and between patients and controls could be confirmed in girls (Table V), and in boys the *z*-value shows a probability of error between $\alpha < 0.1 > 0.05$, only.

TABLE III. Mean Values ($\bar{x} \pm$ SD) of Anthropometric Indices and Their Probabilities of Error in Children With and Without Cleft Lip/Cleft Palate*

Index	Patients		Controls		
	$\bar{x}$	SD	$\bar{x}$	SD	α
Cephalic width/ circumference of head	26.32	1.63	25.38	1.38	<0.01
Cephalic width/ cephalic length	76.94	5.63	74.04	5.01	<0.01
Inner canthal/ outer canthal distance	34.86	4.21	33.37	2.18	<0.01
Inner canthal distance/ circumference of head	5.77	0.65	5.39	0.46	<0.01

*$X^2 = 21.94$; d.f. = 42; $\alpha > 0.99$.

DISCUSSION

Cleft lip/cleft palate as well as IMVs and PHVs are well defined clinical conditions resulting from impaired morphogenesis and phenogenesis, respectively. Because the latter occur late in embryogenesis and, particularly, in fetogenesis, it is highly unlikely that in nonsyndromal vertical facial clefts the number of these morphogenetic variants would be elevated.

This hypothesis can be confirmed in the first part of our study. Neither in the patients' group nor in the group of healthy children did we observe differences in the overall manifestation of IMVs. But, in the anthropometric part of our study, to our surprise, significant differences could be calculated in a number of craniofacial and non-craniofacial anomalies. They were small. However, their arithmetic mean values are significant, even if their regression lines did not strongly differ from each other.

At present, we can only speculate on these findings because, to our knowledge, there is no published anthropometric study of non-craniofacial phenogenetic variants on children with non-syndromal cleft lip/cleft palate.

In the *craniofacial* morphogenetic variants the natural history and natural course of the disorder are strictly influenced by surgical treatment. Retrospective analysis does not allow discrimination of these influences. But there is good evidence that surgical intervention leads to an improvement of morphology. Thus, we suggest that without surgical treatment the anthropometric differences would be greater. However, we should not forget that there is an increased mortality in newborn babies and infants without the advent of plastic surgery. In so far, even using the up to date experience of oral surgeons the existence of minimal quantitative abnormalities in children with facial cleft disorder seems to be explainable.

TABLE IV. Mean Values ($\bar{x} \pm SD$) of Non-Craniofacial Phenogenetic Variants in Children With Cleft Lip/Cleft Palate

Parameter/sex	Patients		Controls		
	$\bar{x}$	SD	$\bar{x}$	SD	α
				Circumference of chest (mm)	
Male	535.94	33.88	557.28	22.13	<0.001
Female	541.18	33.46	513.76	39.70	<0.001
				Internipple distance (mm)	
Male	128.20	11.93	132.79	10.79	<0.001
Female	134.30	10.81	141.02	10.87	<0.001
				Length of sternum (mm)	
Male	104.86	12.46	103.84	10.91	>0.5
Female	105.10	10.62	105.44	10.91	>0.5
				Length of hand (mm)	
Male	118.93	8.62	122.14	8.05	<0.001
Female	117.73	8.25	129.88	6.46	<0.001
				Length of middle finger (mm)	
Male	47.28	5.13	50.59	4.97	<0.001
Female	49.59	4.63	50.58	4.22	>0.25

TABLE V. Comparison of Parameters for the Probit Regression Analysis of the Circumference of Chest

Sex	Patients	Controls
Males	$y = 3.6929 + 1.8745 \log x$ $r = 0.8398$ d.f. = 16 $\alpha < 0.001$ $z_1 = 1.2207$	$y = 4.1162 + 1.2784 \log x$ $r = 0.7686$ d.f. = 12 $\alpha < 0.001$ $z_2 = 1.0169$
	$z = 1.6719$ *$\alpha < 0.10 > 0.05$*	
Females	$y = 3.7487 + 1.7101 \log x$ $r = 0.8411$ d.f. = 16 $\alpha < 0.001$ $z_1 = 1.2249$	$y = 3.8753 + 1.5470 \log x$ $r = 0.9278$ d.f. = 13 $\alpha < 0.001$ $z_2 = 1.6424$
	$z = 2.7612$ *$\alpha < 0.01$*	

Contrary to that phenomenon the findings of *non-craniofacial* phenogenetic variants are difficult to interpret. A smaller circumference of chest and a smaller internipple distance might be explained on the basis of a reduced nutritional state. But, all of the data concerning body height and body mass are located between the 3rd and the 97th centiles of the national German standard [Pelz, 1995]. Another possibility of the explanation of the diminished truncal measurements might be caused by the repeated nasopharyngeal-bronchopulmonary infections of the children with cleft lip/cleft palate.

The finding of smaller hands might also be imaginable by a temporarily less training effect due to manual activities in the patients. This argument would not convincingly underline this suggestion because , on the average, in boys the smaller size of the hands is evident through all of the age classes as it could be confirmed by regression analysis ($z = 1.9679$; $\alpha < .05$).

An intrinsic influence acting longer than merely during the late blastogenesis and early embryogenesis when the morphogenetic error resulting in cleft lip/cleft palate takes place can not be excluded. Secondary prenatal influences being responsible for the correct morphogenetic fine tuning of the fetus, e.g., fetal movement, might be also taken into consideration. Thus, more detailed knowledge of the common clinical morphogenetic disorder is needed for understanding of its complex natural history.

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APPENDIX

IMVs and PHVs and Their Topographical Distributions in Boys and Girls With Cleft Lip/Cleft Palate (n = 230) and Healthy Children (n = 226)

	Patients with cleft lip/cleft palate		Healthy children	
IMV	girls	boys	girls	boys
Head				
–Prominent occiput	0	2	1	2
–Flat occiput	2	2	0	1
–Prominent forehead	1	0	0	0
–Skin tags	1	0	0	0
Eyes				
–Epicanthus	15	21	26	24
–Telecanthus	1	6	0	0
–Palpebral ptosis	0	0	0	0
–Upward slant of the palpebral fissure	3	1	0	1
–Downward slant of the palpebral fissure	0	2	0	0
–Palpebral coloboma/ cataracta	1	0	0	0
–Synophrys	0	0	0	1
Mouth				
–Lip pits	0	0	0	0
–Bivid uvula	3	0	0	0
–Microgenia	2	0	0	0
–Connnatal teeth	1	2	0	0
Ears				
–Preauricular skin tags	1	3	0	0
–Preauricular sinus	0	0	0	0
–Less shaped auricle	2	1	3	8
–Low set ears	0	0	0	3
Trunk				
–Accessory nipple	0	1	0	0
–Deep sacral dimble	5	3	2	1
–Diastasis recti	0	1	0	0
–Umbilical hernia	3	3	0	1
–Inguinal hernia	1	1	0	1
–Hemangiomata, Naevi Café-aut-lait spots (> 1 cm)	4	4	0	1
Hands				
–Simian crease	2	2	1	2
–Sidney line	0	0	0	0
–Single flexion crease dig. V	1	0	0	0
–Clinodactyly	3	5	5	3
–Partial Syndactyly	0	0	0	0
Feet				
–Partial syndactyly	0	1	0	0
–Vertical sole crease	0	0	0	0
–Prominent heel	0	0	0	0
–Dorsiflexed hallux	0	0	0	0
–Wide distance between toes	0	1	0	0
–Hypoplasia of nails	0	0	0	0
–Polydactyly	0	2	0	0
–Broad hallux	0	0	0	0
Total	52	64	38	49